Duplicate Paper #15

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Assistant Commissioner for Patents
Washington, D.C. 20231

On April 22, 2002

TOWNSEND and TOWNSEND and CREW LLP

By: Rosemarie L. Celli

Signed: Rosemarie L. Celli

PATENT
Attorney Docket No.: 015270-006430US
Client Ref. No.: 228-US-NEW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Anderson et al.

Application No.: 09/471,669

Filed: December 24, 1999

For: BETA-SECRETASE ENZYME COMPOSITIONS AND METHODS

Examiner: Walicka, M.

Art Unit: 1652

AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This amendment is submitted in response to the Office Action mailed October 22, 2001. A petition to extend time for response three months, from February 22, 2002 to April 22, 2002, is submitted herewith. Please amend the above-identified application as follows:

IN THE SPECIFICATION:

Please replace the Cross-Reference to Related Applications section with the following replacement section.

Cross-Reference to Related Applications

This application is a nonprovisional of U.S. Application No. 60/114,408, filed 12/31/1998, now abandoned, U.S. Application No. 60/119,571 filed 2/10/1999, now abandoned, U.S. Application No. 60/139,172 filed 6/15/99, now abandoned, all of which are hereby incorporated herein by reference in their entireties.

Please amend the paragraph beginning at page 2, line 13 as follows.

This invention is directed to a β-secretase protein and in particular to a purified protein characterized by a specific activity of at least about 1.0×10^5 nM/h/μg protein in a MBP-C125sw substrate assay, which is representative β-secretase assay that uses a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (hereinafter referred to as "MBP-C125sw").

Please amend the paragraph beginning at page 9, line 22 as follows.

The term "fragment," when referring to β-secretase of the invention, means a polypeptide which has an amino acid sequence which is the same as part of but not all of the amino acid sequence of full-length β-secretase polypeptide. In the context of the present invention, the full length β-secretase is generally identified as SEQ ID NO: 2, the ORF of the full-length nucleotide sequence; however, according to a discovery of the invention, the naturally occurring active form is probably one or more N-terminal truncated versions, such as amino acids 46-501, 22-501, 58-501 or 63-501; other active forms are C-terminal truncated forms ending between about amino acids 450 and 452. The numbering system used throughout is based on the numbering of the sequence SEQ ID NO: 2.

Please amend the paragraph beginning at line 21 of page 63 as follows.

Recombinant proteins were generated with both the 125 C-terminus amino acids of wild-type APP sequence at the cleavage site (..Val-Lys-Met-Asp-Ala..) (SEQ ID NO: 54) (hereinafter referred to as "MBP-C125 wt") or the "Swedish" double mutation (..Val-Asn-Leu-Asp-Ala..) (SEQ ID NO: 51) (also referred to as "MBP-C125sw"). As shown in FIG. 19, cleavage of the intact MBP-fusion protein results in the generation of a truncated amino-terminal fragment, with the new SW-192 Ab-positive epitope uncovered at the carboxy terminus. This amino-terminal fragment can be recognized on Western blots with the same Ab,

or, quantitatively, using an anti-MBP capture-biotinylated SW-192 reporter sandwich format, as shown in FIG. 19.

IN THE CLAIMS:

Please cancel claims 49 and 50.

48. (Amended) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, or a complementary sequence of any of such nucleotides.

51. (Amended) An expression vector, comprising

the isolated nucleic acid of claim 48; and

operably linked to said nucleic acid, regulatory sequences effective for expression of the nucleic acid in a selected host cell.

58. (Amended) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 2, SEQ ID NO: 43, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 75, a β-secretase protein, or a complementary sequence of such nucleotides under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

60. (Amended) The method of claim 59, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO: 73).

62. (Amended) The method of claim 61, wherein said antibody binds specifically to any of the protein compositions of SEQ ID NO: 2, SEQ ID NO: 43, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 66, SEQ

ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 75, or a β-secretase protein.

63. (Amended) The method of claim 61, wherein said antibody further lacks significant immunoreactivity with a protein having the sequence SEQ ID NO: 2 [1-501].

64. (Amended) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

66. (Amended) The cell of claim 64, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

68. (Amended) The cell of claim 64, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

REMARKS

Claims 48 and 51-69 are pending, claims 49 and 50 having been canceled. Independent claim 48 has been amended as follows. The "β-secretase of any of claims 1-10 or 22-35 or a complementary sequence of any of such nucleotides" has been replaced with "SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, or a complementary sequence of any of such nucleotides." Dependent claim 62 has been amended as follows. "[C]laims 1-11

or 22-36" has been replaced with "SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, or a complementary sequence of any of such nucleotides." Independent claim 64 has been amended as follows. "[A] biologically active β-secretase protein of any of claims 1-11 or 22-36 or a complementary sequence of any of such nucleotides" has been replaced with "SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, or a complementary sequence of any of such nucleotides." Support for the amendment to claims 48, 62, and 64 is found in Figures 1A and 2A, and throughout the specification, *e.g.*, support for SEQ ID NO: 43 is found in Figure 2B and at page 7, lines 5-7 of the specification; support for SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69 is found in Figure 2A, and at page 8, line 4, line 5, and line 7, respectively, of the specification.

The suggested amendments to claims 51 and 66 have been made. Claim 51 has been amended so that it no longer depends from canceled claims 49 and 50. Claim 58 has been amended to recite the β-secretase protein of any one of withdrawn claims 1-10 or 22-35. Claim 60 has been amended to identify P10-P4'staD->V by its SEQ ID NO. Claims 62 and 63 have been amended to depend from claim 61. Claim 62 has been further amended to recite the β-secretase protein of any one of withdrawn claims 1-11 or 22-36.

Claim 68 has been amended to recite the full names of MBP-C125wt and MBP-C125sw. The paragraph beginning at page 2, line 13 of the specification has been amend to recite the full name of MBP-C125sw, and the paragraph beginning at line 21 of page 63 of the specification has been amended to recite the full name of MBP-C125wt. Support for these amendments is found at page 63, lines 9-27. The paragraph beginning at line 21 of page 63 of the specification has been amended to recite the sequence identifiers for MBP-C125wt cleavage site and the MBP-C125sw cleavage site, SEQ ID NO: 54 and SEQ ID NO: 51, respectively.

The Cross Reference To Related Applications section has been replaced with a replacement section, which provides the current status of the priority applications. The suggested amendment to the paragraph beginning at page 9, line 22 has been made.

No amendment should be construed as an acquiescence in any ground of rejection. The paragraph numbering of the office action is used in responding to the office action's comments.

1. *Objections*

1.1 Specification

The Office Action has objected to the specification because it lacks the full names of the β-secretase substrates MBP-C125wt and MBP-C125sw. Amendments to the specification moot this objection. At the first occurrence of the MBP-C125wt, the specification has been amended to recite the full name of MBP-C125wt: a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54. At the first occurrence of the MBP-C125sw, the specification has been amended to recite the full name of MBP-C125sw: a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 51.

The suggested amendment to the paragraph beginning at page 9, line 22 has been made.

1.2 Drawings

Formal drawings will be provided before a Notice of Allowance is mailed for the instant application.

1.3 Claims

The suggested amendments have been made in claims 51 and 66.

2. *Rejections*

2.1 35 U.S.C. § 112, second paragraph

Claims 62 and 63 were rejected for lack of sufficient antecedent basis for "antibody." Claims 62 and 63 have been amended to depend from claim 61 to moot the rejection.

Claim 68 was rejected as being indefinite because both claim 68 and the specification allegedly fail to provide explanations of the abbreviations MBP-C125wt and MBP-C125sw. The Examiner's attention is drawn to page 63, lines 9-27 of the specification,

which discusses the construction of MBP-C125wt and MBP-C125sw, both fusion proteins used as β-secretase substrates in the MBP-C125 assay. Figure 19 schematically shows cleavage of the intact MBP-C125wt and MBP-C125sw fusion proteins. The MBP-C125wt and MBP-C125sw cleavage sites are discussed on page 63, lines 21-23 of the specification. The specification and claim 68 have been amended to recite the full names of MBP-C125wt and MBP-C125sw.

2.2 35 U.S.C. § 112, second paragraph

Independent claim 48, and claims 51-57 depending therefrom have been rejected because the specification allegedly "does not reasonable provide enablement for any β-secretase from any biological source as was as man-made." This rejection is respectfully traversed.

As discussed above, amended independent claim 48 is directed to a sequence of nucleotides encoding "SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, or a complementary sequence of any of such nucleotides." The Office Action acknowledges the specification is enabled for β-secretases having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 43, SEQ ID NO: 58, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69, SEQ ID NO: 74, SEQ ID NO: 75.

2.2 [*sic*] Rejection under 35 U.S.C. § 102(b)

Independent claim 48, and claims 51-57 depending therefrom have been rejected under 102(b) as allegedly being anticipated by Powell *et al.* (EP 0 855 444 A2). This rejection is respectfully traversed.

Anticipation under § 102 requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The "exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference." *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 USPQ 409, 411 (Fed. Cir. 1984). See also MPEP 2131.

Powell *et al.* exclude at least one element that is set forth in Applicants' claims 48 and 51-57. Claims 48 and 51-57 are directed to nucleotide sequences which have a thymine at residue 389 and encode a protein having a valine at residue 130. Powell *et al.* do not disclose such a nucleotide sequence.

It is the Office Action's position the nucleotide sequence (SEQ ID NO: 1) and the amino acid sequence (SEQ ID NO: 2) disclosed by Powell *et al.* are identical to SEQ ID NO: 1 and SEQ ID NO: 2, respectively, of the instant application. Applicants respectfully point out that the SEQ ID NO: 1 disclosed in the instant application differs from SEQ ID NO: 1 disclosed by Powell *et al.* at nucleotide 389. The instant application discloses a thymine residue at position 389, while Powel *et al.* disclose an adenine residue at position 389. (*See* Exhibit 1, attached hereto.) Further, Applicants respectfully point out that the SEQ ID NO: 2 disclosed in the instant application differs from SEQ ID NO: 2 disclosed by Powell *et al.* at amino acid 130. The instant application discloses a valine residue at position 130, while Powel *et al.* disclose an glutamic acid residue at position 130. (*See* Exhibit 2, attached hereto.) Applicants note that neither the query sequence or the database sequence used to prepare the sequence alignment attached to the Office Action is identical to SEQ ID NO: 2 disclosed by Powell *et al.*

The failure of Powell *et al.* to teach SEQ ID NO: 1 and SEQ ID NO: 2 of the present application precludes an anticipation rejection based on this reference. Therefore, the rejection should be withdrawn.

2.3 Rejection under 35 U.S.C. § 103(a)

Claims 58-59 and 61-63 are rejected as allegedly being unpatentable over Powell *et al.* (EP 0855 444) and further in view of Harakas. The rejection is respectfully traversed.

As discussed above, Powell *et al.* do not teach SEQ ID NO: 1 and SEQ ID NO: 2 of the present application. As acknowledged in the Office Action, Powell *et al.* do not teach recovering β-secretase from a culture of host cells capable of producing β-secretase. The

Office Action states "Harakas teaches that affinity matrices may contain as a biospecific ligands enzyme inhibitors or antibodies [*sic*]."

The citation of Powell *et al.* or Powell *et al.* further in view of Harakas does not establish a *prima facie* case of obviousness. Obviousness requires either that the "references must expressly or impliedly suggest the claimed combination or the Examiner must present a convincing line of reasoning as to why the invention would have been obvious in light of the teachings of the references." *Ex Parte Clapp*, 227 USPQ 972, 973 (BPAI 1985). The Examiner must consider "all of the facts." *In re Lunsford*, 148 USPQ 721, 725 (CCPA 1966). The Examiner is not free to "pick and choose" prior art that supports his position. *Akzo v. US International Trade Commission*, 1 USPQ2d at 1241, 1246 (Fed. Cir. 1986). Obviousness is not established where the prior art as a whole "gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

The Powell *et al.* reference does not expressly or impliedly suggest the claimed invention. Powell *et al.* do not teach recovering β-secretase from a culture of host cells capable of producing β-secretase. The Harakas reference does not expressly or impliedly suggest the claimed invention. Harakas contains no discussion whatever of separating β-secretase from an extract or culture media containing using an affinity matrix. Harakas similarly fails to disclose or suggest use of a β-secretase inhibitor, or an antibody characterized by its ability to bind β-secretase as recited in the present claims.

The motivation asserted by the Examiner for combining the references would have been insufficient to have led one to use an affinity matrix for separation of β-secretase from cell extract or cultured medium, when an affinity matrix is considered as but one choice from a vast repertoire of potential purification procedures. It is well known that the purification of a protein is not an exact science and that any strategy has potential advantages and disadvantages, the full significance of which are unpredictable without empirical experimentation. The advantage of affinity chromatography identified by Harakas would not have appeared to have any particular relevance to separation of β-secretase from cell extract or cultured medium, and would not have motivated the selection of affinity chromatography from

the vast repertoire of available purification methods available. Even assuming *arguendo* that one were motivated to combine the teachings of the cited references, their combination would not have provided a method of separating β-secretase from cell extract or cultured medium, as claimed.

Perhaps recognizing the deficiencies of Powell *et al.* and Harakas, the Examiner attempts to supplement its teaching by imputing additional information to one of ordinary skill that would "further modify the β-secretases" disclosed by Powell *et al.* "by using for purification an affinity matrix method, when the biospecific ligand is a Powell *et al.* inhibitor or antibody. This line of reasoning is unconvincing. The Examiner's position fails to comprehend, *inter alia*, the almost infinite variety of "choices" potentially available, and the failure of the art to provide any guidance for selecting among these choices other than by empirical experimentation. There is, of course, an entire literature of laboratory manuals, textbooks and journal articles devoted to purification of proteins, of which the cited Harakas reference forms a minute part. A brief glance at this literature would have revealed a vast repertoire of potential purification procedures such as precipitation, anion-exchange chromatography, gel filtration, chromatography on hydroxyapatite columns, hydrophobic chromatography, chromatography on immobilized reactive dyes, affinity chromatography, chromatofocusing, and high-performance liquid chromatography. Each of these procedures in turn has numerous variations. From this vast repertoire of potential techniques, the Examiner has failed to identify any reason that one would have selected an affinity matrix for separation of β-secretase from cell extract or cultured medium.

For all of the above reasons, it is respectfully submitted that the Examiner's rejection is erroneous and should be reversed.

2.4 Non-statutory double patenting

Claim 50 has been canceled rendering the provisional rejection moot.

2.5 Statutory double patenting

Claims 48, 51-62 and 64-59 are provisionally rejected under obviousness-type double patenting as allegedly being unpatentable over claims 56 and 61-77 of copending application 09/501,708.

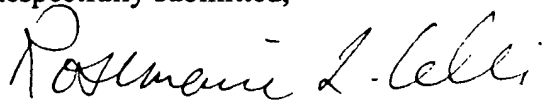
If, upon allowance, the claims of the 09/501,708 application are in conflict with the presently claimed invention, Applicants will address the provisional rejection of claims 48, 51-62 and 64-59 under non-statutory obviousness-type double patenting.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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PA 3215247 v3

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please replace the CROSS REFERENCE TO RELATED APPLICATIONS section with the following replacement section.

Cross-Reference to Related Applications

This application is a nonprovisional[claims the benefit] of U.S. [Provisional]Application No.[Numbers] 60/114,408, filed 12/31/1998, now abandoned, U.S. Application No. 60/119,571 filed 2/10/1999, now abandoned, U.S. Application No. 60/139,172 filed 6/15/99, now abandoned, all of which are hereby incorporated herein by reference in their entireties.

Please amend the paragraph beginning at page 2, line 13 as follows.

This invention is directed to a β-secretase protein and in particular to a purified protein characterized by a specific activity of at least about 1.0×10^5 nM/h/μg protein in a MBP-C125sw substrate assay, which is representative β-secretase assay that uses a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (hereinafter referred to as "MBP-C125sw").

Please amend the paragraph beginning at page 9, line 22 as follows.

The term "fragment," when referring to β-secretase of the invention, means a polypeptide which has an amino acid sequence which is the same as part of but not all of the amino acid sequence of full-length β-secretase polypeptide. In the context of the present invention, the full length β-secretase is generally identified as SEQ ID NO: 2, the ORF of the full-length nucleotide sequence; however, according to a discovery of the invention, the naturally occurring active form is probably one or more N-terminal truncated versions, such as amino acids 46-501, 22-501, 58-501 or 63-501; other active forms are C-terminal truncated forms ending between about amino acids 450 and 452. The numbering system used throughout is based on the numbering of the sequence SEQ ID NO: 2.

Please amend the paragraph beginning at line 21 of page 63 as follows.

Recombinant proteins were generated with both the 125 C-terminus amino acids of wild-type APP sequence [(MBP-C125 wt)] at the cleavage site (..Val-Lys-Met-Asp-Ala..) (SEQ ID NO: 54) (hereinafter referred to as "MBP-C125wt") or the "Swedish" double mutation [(MBP-C125sw)] (..Val-Asn-Leu-Asp-Ala..) (SEQ ID NO: 51) (also referred to as "MBP-C125sw"). As shown in FIG. 19, cleavage of the intact MBP-fusion protein results in the generation of a truncated amino-terminal fragment, with the new SW-192 Ab-positive epitope uncovered at the carboxy terminus. This amino-terminal fragment can be recognized on Western blots with the same Ab, or, quantitatively, using an anti-MBP capture-biotinylated SW-192 reporter sandwich format, as shown in FIG. 19.

IN THE CLAIMS:

Please amend the claims as follows.

48. (Amended) An isolated nucleic acid, comprising a sequence of nucleotides that encodes SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69,[the β-secretase protein of any of claims 1-10 or 22-35,] or a complementary sequence of any of such nucleotides.

51. (Amended) An expression vector, comprising

the isolated nucleic acid of claim 48[, 49 or 50]; and

operably linked to said nucleic acid, regulatory sequences effective for expression of the nucleic acid in a selected host cell.

58. (Amended) A method of producing a recombinant β-secretase enzyme, comprising culturing a cell transfected with a vector comprising a sequence of nucleotides that encodes SEQ ID NO: 2, SEQ ID NO: 43, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 75, a β-secretase protein, or a complementary sequence of such nucleotides[according to any of claims 53-57]

under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

60. The method of claim 59, wherein said inhibitor molecule is P10-P4'staD->V (SEQ ID NO: 73).

62. (Amended) The method of claim 61[58], wherein said antibody binds specifically to any of the protein compositions of SEQ ID NO: 2, SEQ ID NO: 43, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 74, SEQ ID NO: 75, or a β-secretase protein[claims 1-11 or 22-36].

63. (Amended) The method of claim 61[58], wherein said antibody further lacks significant immunoreactivity with a protein having the sequence SEQ ID NO: 2 [1-501].

64. (Amended) A heterologous cell, comprising

(i) a nucleic acid molecule encoding SEQ ID NO: 43, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 69,[a biologically active β-secretase protein according to any of claims 1-11 or 22-36,] or the complementary sequence of said nucleic acid molecule;

(ii) a nucleic acid molecule encoding a β-secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecules in said cell.

66. (Amended) The cell of claim 64, wherein both said nucleic acids encoding said β-secretase protein and encoding said β-secretase substrate molecule are heterologous to said cell.

68. (Amended) The cell of claim 64, wherein said β-secretase substrate is selected from the group consisting of a maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54

(MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw).

P1633

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PTO/SB/21 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/471,669
Filing Date	December 24, 1999
First Named Inventor	Anderson, John P.
Group Art Unit	1633
Examiner Name	Nikodem, D.
Total Number of Pages in This Submission: 51	Attorney Docket Number: 015270-006430US

COPY OF PAPERS ORIGINALLY FILED

ENCLOSURES *(check all that apply)*

- [X] Fee Transmittal Form (1 page, submitted in duplicate)
- [ ] Fee Attached
- [X] Amendment (15 pages w/ attached Exhibit 1 (24 pages) and Exhibit 2 (7 pages)
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [X] Extension of Time Request (1 page)
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Assignment Papers *(for an Application)*
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s)
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Other Enclosure(s) *(please identify below)*:

Return Postcard

Remarks: The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm and Individual name	Townsend and Townsend and Crew LLP Rosemarie L. Celli Reg. No. 42,397
Signature	Rosemarie L. Celli
Date	April 22, 2002

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: April 22, 2002

Typed or printed name	Rosemarie L. Celli		
Signature	Rosemarie L. Celli	Date	April 22, 2002

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PA 3216866 v1

PTO/SB/17 (09-00)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

Complete if Known	
Application Number	09/471,669
Filing Date	December 24, 1999
First Named Inventor	Anderson, John P.
Examiner Name	Nikodem, D.
Group Art Unit	1633
Attorney Docket No.	015270-006430US

TOTAL AMOUNT OF PAYMENT ($) 920

METHOD OF PAYMENT

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 20-1430

Deposit Account Name: Townsend and Townsend and Crew LLP

☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☐ **Payment Enclosed:**

☐ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Large Entity Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES

			Extra Claims		Fee from below		Fee Paid
Total Claims		-20**	=	X		=	
Independent Claims		-3**	=	X		=	
Multiple Dependent				X		=	

Large Fee Code	Large Entity Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Fee Code	Large Entity Fee ($)	Small Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	920
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR § 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify)					

The Commissioner is authorized to charge any additional fees to the above noted Deposit Account.

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)920

SUBMITTED BY				Complete (if applicable)	
Name (Print/Type)	Rosemarie L. Celli	Registration No. (Attorney/Agent)	42,397	Telephone	650-326-2400
Signature	Rosemarie L. Celli			Date	April 22, 2002

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231. PA 3216591 v1

PTO/SB/22 (10-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 015270-006430US

In re Application of John Anderson, et al.

Application Number 09/471,669 | Filed December 24, 1999

For BETA-SECRETASE ENZYME COMPOSITIONS AND METHODS

Group Art Unit 1633 | Examiner Nikodem, D.

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $
- ☐ Two months (37 CFR 1.17(a)(2)) $
- ☒ Three months (37 CFR 1.17(a)(3)) $920
- ☐ Four months (37 CFR 1.17(a)(4)) $
- ☐ Five months (37 CFR 1.17(a)(5)) $

- ☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $.
- ☐ A check in the amount of the fee is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Commissioner has already been authorized to charge fees in this application to a Deposit Account.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

I have enclosed a duplicate copy of this sheet.

I am the ☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71

Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record.

☐ attorney or agent under 37 CFR 1.34(a).

Registration number if acting under 37 CFR 1.34(a). _____ .

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

April 22, 2002
Date

Rosemarie L Celli
Signature

Rosemarie L. Celli, Reg. No. 42,397
Typed or printed name

05/02/2002 RMEBRAHT 00000126 201430 09471669

01 FC:117 920.00 CH

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

PA 3216580 v1

DIALIGN 2.1
****

Developed by Burkhard Morgenstern, Said Abdeddaim, Kornelie Frech,
Klaus Hahn, Thomas Werner, Jens Stoye, Andreas Dress

e-mail: burkhard.morgenstern@rp-rorer.co.uk

Published research assisted by DIALIGN 2 should cite:

B. Morgenstern (1999),
"DIALIGN 2: improvement of the segment-to-segment
approach to multiple sequence alignment."
Bioinformatics 15, 203 - 210.

Options:
========

1) nucleic acid sequences aligned
2) no translation of of nucleotide diagonals into peptide diagonals
3) 5 "*" characters for regions of maximum similarity

Aligned sequences:	length:
1) EP	2541
2) 09/471,669	1503

Average sequence length: 2022.000

Please note that only upper-case letters are considered to be aligned.
For more information, have a look at the user guide

EXHIBIT 1

http://bibiserv.techfak.uni-bielefeld.de/dialign/user_guide2.html

Alignment (DIALIGN format):
==========

```
EP              1   ATGGCCCAAG CCCTGCCCTG GCTCCTGCTG TGGATGGGC
G CGGGAGTGCT
09/471,669      1   ATGGCCCAAG CCCTGCCCTG GCTCCTGCTG TGGATGGGC
G CGGGAGTGCT

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EP             51   GCCTGCCCAC GGCACCCAGC ACGGCATCCG GCTGCCCCT
G CGCAGCGGCC
09/471,669     51   GCCTGCCCAC GGCACCCAGC ACGGCATCCG GCTGCCCCT
G CGCAGCGGCC

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EXHIBIT 1

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EP          101    TGGGGGGCGC CCCCCTGGGG CTGCGGCTGC CCCGGGAGA
C CGACGAAGAG
09/471,669  101    TGGGGGGCGC CCCCCTGGGG CTGCGGCTGC CCCGGGAGA
C CGACGAAGAG

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EP          151    CCCGAGGAGC CCGGCCGGAG GGGCAGCTTT GTGGAGATG
G TGGACAACCT
09/471,669  151    CCCGAGGAGC CCGGCCGGAG GGGCAGCTTT GTGGAGATG
G TGGACAACCT

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EP          201    GAGGGGCAAG TCGGGGCAGG GCTACTACGT GGAGATGAC
C GTGGGCAGCC
09/471,669  201    GAGGGGCAAG TCGGGGCAGG GCTACTACGT GGAGATGAC
C GTGGGCAGCC

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EP            251   CCCCGCAGAC GCTCAACATC CTGGTGGATA CAGGCAGCA
G TAACTTTGCA
09/471,669    251   CCCCGCAGAC GCTCAACATC CTGGTGGATA CAGGCAGCA
G TAACTTTGCA


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EP            301   GTGGGTGCTG CCCCCCACCC CTTCCTGCAT CGCTACTAC
C AGAGGCAGCT
09/471,669    301   GTGGGTGCTG CCCCCCACCC CTTCCTGCAT CGCTACTAC
C AGAGGCAGCT


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EXHIBIT 1

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EP          351   GTCCAGCACA TACCGGGACC TCCGGAAGGG TGTGTATGa
G CCCTACACCC
09/471,669  351   GTCCAGCACA TACCGGGACC TCCGGAAGGG TGTGTATGt
G CCCTACACCC

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EP          401   AGGGCAAGTG GGAAGGGGAG CTGGGCACCG ACCTGGTAA
G CATCCCCCAT
09/471,669  401   AGGGCAAGTG GGAAGGGGAG CTGGGCACCG ACCTGGTAA
G CATCCCCCAT

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EP          451   GGCCCCAACG TCACTGTGCG TGCCAACATT GCTGCCATC
A CTGAATCAGA
09/471,669  451   GGCCCCAACG TCACTGTGCG TGCCAACATT GCTGCCATC
A CTGAATCAGA

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EP            501   CAAGTTCTTC ATCAACGGCT CCAACTGGGA AGGCATCCT
G GGGCTGGCCT
09/471,669    501   CAAGTTCTTC ATCAACGGCT CCAACTGGGA AGGCATCCT
G GGGCTGGCCT

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EP            551   ATGCTGAGAT TGCCAGGCCT GACGACTCCC TGGAGCCTT
T CTTTGACTCT
09/471,669    551   ATGCTGAGAT TGCCAGGCCT GACGACTCCC TGGAGCCTT
T CTTTGACTCT

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EP            601   CTGGTAAAGC AGACCCACGT TCCCAACCTC TTCTCCCTG
C AGCTTTGTGG
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EXHIBIT 1

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09/471,669  601    CTGGTAAAGC AGACCCACGT TCCCAACCTC TTCTCCCTG
C AGCTTTGTGG

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EP           651   TGCTGGCTTC CCCCTCAACC AGTCTGAAGT GCTGGCCTC
T GTCGGAGGGA
09/471,669  651    TGCTGGCTTC CCCCTCAACC AGTCTGAAGT GCTGGCCTC
T GTCGGAGGGA

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EP           701   GCATGATCAT TGGAGGTATC GACCACTCGC TGTACACAG
G CAGTCTCTGG
09/471,669  701    GCATGATCAT TGGAGGTATC GACCACTCGC TGTACACAG
G CAGTCTCTGG

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EP          751     TATACACCCA TCCGGCGGGA GTGGTATTAT GAGGTGATC
A TTGTGCGGGT
09/471,669  751     TATACACCCA TCCGGCGGGA GTGGTATTAT GAGGTGATC
A TTGTGCGGGT


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EP          801     GGAGATCAAT GGACAGGATC TGAAAATGGA CTGCAAGGA
G TACAACTATG
09/471,669  801     GGAGATCAAT GGACAGGATC TGAAAATGGA CTGCAAGGA
G TACAACTATG


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EP          851     ACAAGAGCAT TGTGGACAGT GGCACCACCA ACCTTCGTT
T GCCCAAGAAA
09/471,669  851     ACAAGAGCAT TGTGGACAGT GGCACCACCA ACCTTCGTT
T GCCCAAGAAA
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EP            901   GTGTTTGAAG CTGCAGTCAA ATCCATCAAG GCAGCCTCC
T CCACGGAGAA
09/471,669    901   GTGTTTGAAG CTGCAGTCAA ATCCATCAAG GCAGCCTCC
T CCACGGAGAA


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EP            951   GTTCCCTGAT GGTTTCTGGC TAGGAGAGCA GCTGGTGTG
C TGGCAAGCAG
09/471,669    951   GTTCCCTGAT GGTTTCTGGC TAGGAGAGCA GCTGGTGTG
C TGGCAAGCAG


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EP          1001    GCACCACCCC TTGGAACATT TTCCCAGTCA TCTCACTCT
A CCTAATGGGT
09/471,669 1001     GCACCACCCC TTGGAACATT TTCCCAGTCA TCTCACTCT
A CCTAATGGGT

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EP          1051    GAGGTTACCA ACCAGTCCTT CCGCATCACC ATCCTTCCG
C AGCAATACCT
09/471,669 1051     GAGGTTACCA ACCAGTCCTT CCGCATCACC ATCCTTCCG
C AGCAATACCT

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EP          1101    GCGGCCAGTG GAAGATGTGG CCACGTCCCA AGACGACTG
T TACAAGTTTG
09/471,669 1101     GCGGCCAGTG GAAGATGTGG CCACGTCCCA AGACGACTG
T TACAAGTTTG
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EP          1151    CCATCTCACA GTCATCCACG GGCACTGTTA TGGGAGCTG
T TATCATGGAG
09/471,669 1151     CCATCTCACA GTCATCCACG GGCACTGTTA TGGGAGCTG
T TATCATGGAG

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EP          1201    GGCTTCTACG TTGTCTTTGA TCGGGCCCGA AAACGAATT
G GCTTTGCTGT
09/471,669 1201     GGCTTCTACG TTGTCTTTGA TCGGGCCCGA AAACGAATT
G GCTTTGCTGT

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EP          1251    CAGCGCTTGC CATGTGCACG ATGAGTTCAG GACGGCAGC
G GTGGAAGGCC
09/471,669 1251     CAGCGCTTGC CATGTGCACG ATGAGTTCAG GACGGCAGC
G GTGGAAGGCC

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EP          1301    CTTTTGTCAC CTTGGACATG GAAGACTGTG GCTACAACA
T TCCACAGACA
09/471,669 1301     CTTTTGTCAC CTTGGACATG GAAGACTGTG GCTACAACA
T TCCACAGACA

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EP          1351    GATGAGTCAA CCCTCATGAC CATAGCCTAT GTCATGGCT
G CCATCTGCGC
09/471,669 1351     GATGAGTCAA CCCTCATGAC CATAGCCTAT GTCATGGCT
G CCATCTGCGC

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EP          1401    CCTCTTCATG CTGCCACTCT GCCTCATGGT GTGTCAGTG
G CGCTGCCTCC
09/471,669 1401     CCTCTTCATG CTGCCACTCT GCCTCATGGT GTGTCAGTG
G CGCTGCCTCC


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EP          1451    GCTGCCTGCG CCAGCAGCAT GATGACTTTG CTGATGACA
T CTCCCTGCTG
09/471,669 1451     GCTGCCTGCG CCAGCAGCAT GATGACTTTG CTGATGACA
T CTCCCTGCTG


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EP          1501    AAGtgaggag gcccatggga gaaagataga gattcccct
g ggaccacacc
09/471,669 1501     AAG------- ---------- ---------- ---------
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EP          1551    tccgtggttc actttggtca caagtaggag acacagatg
g cacctgtggc
09/471,669 1504     ---------- ---------- ---------- ---------
- ----------

EP          1601    cagagcacct caggaccctc cccacccacc aaatgcctc
t gccttgatgg
09/471,669 1504     ---------- ---------- ---------- ---------
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EXHIBIT 1

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EP          1651    agaaggaaaa ggctggcaag gtgggttcca gggactgta
c ctgtaggaaa
09/471,669 1504     ---------- ---------- ---------- ---------
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EP          1701    cagaaaagag aagaaagaag cactctgctg gcgggaata
c tcttggtcac
09/471,669 1504     ---------- ---------- ---------- ---------
- ----------
```

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EP          1751    ctcaaattta agtcgggaaa ttctgctgct tgaaacttc
a gccctgaacc
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EXHIBIT 1

09/471,669 1504 ---------- ---------- ---------- ---------
- ----------

EP 1801 tttgtccacc attcctttaa attctccaac ccaaagtat
t cttctttttct
09/471,669 1504 ---------- ---------- ---------- ---------
- ----------

EP 1851 tagtttcaga agtactggca tcacacgcag gttaccttg
g cgtgtgtccc
09/471,669 1504 ---------- ---------- ---------- ---------
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EXHIBIT 1

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EP          1901    tgtggtaccc gggcagagaa gagaccaagc ttgtttccc
t gctggccaaa
09/471,669 1504     ---------- ---------- ---------- ---------
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EP          1951    gtcagtagga gaggatgcac agtttgctat ttgctttag
a gacagggact
09/471,669 1504     ---------- ---------- ---------- ---------
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EP          2001    gtataaacaa gcctaacatt ggtgcaaaga ttgcctctt
g aattaaaaaa
09/471,669 1504     ---------- ---------- ---------- ---------
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EXHIBIT 1

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EP          2051    aaaaactaga ttgactattt atacaaatgg gggcggctg
g aaagaggaga
09/471,669 1504     ---------- ---------- ---------- ---------
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```

```
EP          2101    aggagaggga gtacaaagac agggaatagt gggatcaaa
g ctaggaaagg
09/471,669 1504     ---------- ---------- ---------- ---------
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```


EXHIBIT 1

```
EP          2151    cagaaacaca accactcacc agtcctagtt ttagacctc
a tctccaagat
09/471,669 1504     ---------- ---------- ---------- ---------
- ----------
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```
EP          2201    agcatcccat ctcagaagat gggtgttgtt ttcaatgtt
t tcttttctgt
09/471,669 1504     ---------- ---------- ---------- ---------
- ----------
```

```
EP          2251    ggttgcagcc tgaccaaaag tgagatggga agggcttat
c tagccaaaga
09/471,669 1504     ---------- ---------- ---------- ---------
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```


EXHIBIT 1

```
EP          2301    gctctttttt agctctctta aatgaagtgc ccactaagg
a agttccactt
09/471,669 1504     ---------- ---------- ---------- ---------
- ----------

EP          2351    gaacacatgg aatttctgcc atattaattt ccattgtct
c tatctggaac
09/471,669 1504     ---------- ---------- ---------- ---------
- ----------
```


EXHIBIT 1

```
EP          2401    cacccttttaa tctctacata tgattaggtc cagcacttg
a aaatattcct
09/471,669 1504     ---------- ---------- ---------- ---------
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EP          2451    aaccnnaatt tgncttgggg gctttgcngn ccaggtgct
a aaagggnttg
09/471,669 1504     ---------- ---------- ---------- ---------
- ----------

EP          2501    ggtaggngnc cncttntatn tnatncctna aaaggttan
n g
09/471,669 1504     ---------- ---------- ---------- ---------
- -
```


EXHIBIT 1

Alignment (FASTA format):
==========

>EP
ATGGCCCAAGCCCTGCCCTGGCTCCTGCTGTGGATGGGCGCGGGAGTGCT
GCCTGCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCC
TGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAG
CCCGAGGAGCCCGGCCGGAGGGGCAGCTTTGTGGAGATGGTGGACAACCT
GAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAGATGACCGTGGGCAGCC
CCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACTTTGCA
GTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCT
GTCCAGCACATACCGGGACCTCCGGAAGGGTGTGTATGaGCCCTACACCC
AGGGCAAGTGGGAAGGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCAT
GGCCCCAACGTCACTGTGCGTGCCAACATTGCTGCCATCACTGAATCAGA
CAAGTTCTTCATCAACGGCTCCAACTGGGAAGGCATCCTGGGGCTGGCCT
ATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGACTCT
CTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGG
TGCTGGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGA
GCATGATCATTGGAGGTATCGACCACTCGCTGTACACAGGCAGTCTCTGG
TATACACCCATCCGGCGGGAGTGGTATTATGAGGTGATCATTGTGCGGGT
GGAGATCAATGGACAGGATCTGAAAATGGACTGCAAGGAGTACAACTATG
ACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCCAAGAAA
GTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAA
GTTCCCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAG
GCACCACCCCTTGGAACATTTTCCCAGTCATCTCACTCTACCTAATGGGT
GAGGTTACCAACCAGTCCTTCCGCATCACCATCCTTCCGCAGCAATACCT
GCGGCCAGTGGAAGATGTGGCCACGTCCCAAGACGACTGTTACAAGTTTG
CCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATCATGGAG
GGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGT
CAGCGCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCC
CTTTTGTCACCTTGGACATGGAAGACTGTGGCTACAACATTCCACAGACA
GATGAGTCAACCCTCATGACCATAGCCTATGTCATGGCTGCCATCTGCGC
CCTCTTCATGCTGCCACTCTGCCTCATGGTGTGTCAGTGGCGCTGCCTCC
GCTGCCTGCGCCAGCAGCATGATGACTTTGCTGATGACATCTCCCTGCTG

EXHIBIT 1

AAGtgaggaggcccatgggagaaagatagagattcccctgggaccacacc
tccgtggttcactttggtcacaagtaggagacacagatggcacctgtggc
cagagcacctcaggaccctccccacccaccaaatgcctctgccttgatgg
agaaggaaaaggctggcaaggtgggttccagggactgtacctgtaggaaa
cagaaaagagaagaaagaagcactctgctggcgggaatactcttggtcac
ctcaaatttaagtcgggaaattctgctgcttgaaacttcagccctgaacc
tttgtccaccattcctttaaattctccaacccaaagtattcttcttttct
tagtttcagaagtactggcatcacacgcaggttaccttggcgtgtgtccc
tgtggtacccgggcagagaagagaccaagcttgtttccctgctggccaaa
gtcagtaggagaggatgcacagtttgctatttgctttagagacagggact
gtataaacaagcctaacattggtgcaaagattgcctcttgaattaaaaaa
aaaaactagattgactatttatacaaatgggggcggctggaaagaggaga
aggagagggagtacaaagacagggaatagtgggatcaaagctaggaaagg
cagaaacacaaccactcaccagtcctagttttagacctcatctccaagat
agcatcccatctcagaagatgggtgttgttttcaatgttttcttttctgt
ggttgcagcctgaccaaaagtgagatgggaagggcttatctagccaaaga
gctctttttttagctctcttaaatgaagtgcccactaaggaagttccactt
gaacacatggaatttctgccatattaatttccattgtctctatctggaac
caccctttaatctctacatatgattaggtccagcacttgaaaatattcct
aaccnnaatttgncttgggggctttgcngnccaggtgctaaaagggnttg
ggtaggngnccnctttntatntnatnccctnaaaaggttannng

>09/471,669
ATGGCCCAAGCCCTGCCCTGGCTCCTGCTGTGGATGGGCGCGGGAGTGCT
GCCTGCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGCGGCC
TGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGGAGACCGACGAAGAG
CCCGAGGAGCCCGGCCGGAGGGGCAGCTTTGTGGAGATGGTGGACAACCT
GAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAGATGACCGTGGGCAGCC
CCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACTTTGCA
GTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCAGCT
GTCCAGCACATACCGGGACCTCCGGAAGGGTGTGTATGtGCCCTACACCC
AGGGCAAGTGGGAAGGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCAT
GGCCCCAACGTCACTGTGCGTGCCAACATTGCTGCCATCACTGAATCAGA
CAAGTTCTTCATCAACGGCTCCAACTGGGAAGGCATCCTGGGGCTGGCCT
ATGCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGACTCT
CTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGG
TGCTGGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGA
GCATGATCATTGGAGGTATCGACCACTCGCTGTACACAGGCAGTCTCTGG
TATACACCCATCCGGCGGGAGTGGTATTATGAGGTGATCATTGTGCGGGT
GGAGATCAATGGACAGGATCTGAAAATGGACTGCAAGGAGTACAACTATG
ACAAGAGCATTGTGGACAGTGGCACCACCAACCTTCGTTTGCCCAAGAAA
GTGTTTGAAGCTGCAGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAA
GTTCCCTGATGGTTTCTGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAG
GCACCACCCCTTGGAACATTTTCCCAGTCATCTCACTCTACCTAATGGGT
GAGGTTACCAACCAGTCCTTCCGCATCACCATCCTTCCGCAGCAATACCT
GCGGCCAGTGGAAGATGTGGCCACGTCCCAAGACGACTGTTACAAGTTTG

EXHIBIT 1

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CCATCTCACAGTCATCCACGGGCACTGTTATGGGAGCTGTTATCATGGAG
GGCTTCTACGTTGTCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGT
CAGCGCTTGCCATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCC
CTTTTGTCACCTTGGACATGGAAGACTGTGGCTACAACATTCCACAGACA
GATGAGTCAACCCTCATGACCATAGCCTATGTCATGGCTGCCATCTGCGC
CCTCTTCATGCTGCCACTCTGCCTCATGGTGTGTCAGTGGCGCTGCCTCC
GCTGCCTGCGCCAGCAGCATGATGACTTTGCTGATGACATCTCCCTGCTG
AAG-----------------------------------------------
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EXHIBIT 1

DIALIGN 2.1
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Developed by Burkhard Morgenstern, Said Abdeddaim, Kornelie Frech,
Klaus Hahn, Thomas Werner, Jens Stoye, Andreas Dress

e-mail: burkhard.morgenstern@rp-rorer.co.uk

Published research assisted by DIALIGN 2 should cite:

B. Morgenstern (1999),
"DIALIGN 2: improvement of the segment-to-segment
approach to multiple sequence alignment."
Bioinformatics 15, 203 - 210.

Options:
========

1) proteine sequences aligned
2) 5 "*" characters for regions of maximum similarity

Aligned sequences:		length:
1)	855444	501
2)	2	501

Average sequence length: 501.000

Please note that only upper-case letters are considered to be aligned.
For more information, have a look at the user guide

http://bibiserv.techfak.uni-bielefeld.de/dialign/user_gu

EXHIBIT 2

ide2.html

Alignment (DIALIGN format):
==========

```
855444          1   MAQALPWLLL WMGAGVLPAH GTQHGIRLPL RSGLGGAPL
G LRLPRETDEE
2               1   MAQALPWLLL WMGAGVLPAH GTQHGIRLPL RSGLGGAPL
G LRLPRETDEE

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855444         51   PEEPGRRGSF VEMVDNLRGK SGQGYYVEMT VGSPPQTLN
I LVDTGSSNFA
2              51   PEEPGRRGSF VEMVDNLRGK SGQGYYVEMT VGSPPQTLN
I LVDTGSSNFA

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EXHIBIT 2

```
855444       101   VGAAPHPFLH RYYQRQLSST YRDLRKGVYE PYTQGKWEG
E LGTDLVSIPH
2            101   VGAAPHPFLH RYYQRQLSST YRDLRKGVYV PYTQGKWEG
E LGTDLVSIPH

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855444       151   GPNVTVRANI AAITESDKFF INGSNWEGIL GLAYAEIAR
P DDSLEPFFDS
2            151   GPNVTVRANI AAITESDKFF INGSNWEGIL GLAYAEIAR
P DDSLEPFFDS

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855444       201   LVKQTHVPNL FSLQLCGAGF PLNQSEVLAS VGGSMIIGG
I DHSLYTGSLW
2            201   LVKQTHVPNL FSLQLCGAGF PLNQSEVLAS VGGSMIIGG
I DHSLYTGSLW

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EXHIBIT 2

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855444       251    YTPIRREWYY EVIIVRVEIN GQDLKMDCKE YNYDKSIVD
S GTTNLRLPKK
2            251    YTPIRREWYY EVIIVRVEIN GQDLKMDCKE YNYDKSIVD
S GTTNLRLPKK

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855444       301    VFEAAVKSIK AASSTEKFPD GFWLGEQLVC WQAGTTPWN
I FPVISLYLMG
2            301    VFEAAVKSIK AASSTEKFPD GFWLGEQLVC WQAGTTPWN
I FPVISLYLMG

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855444       351    EVTNQSFRIT ILPQQYLRPV EDVATSQDDC YKFAISQSS
T GTVMGAVIME
```


EXHIBIT 2

```
2              351   EVTNQSFRIT ILPQQYLRPV EDVATSQDDC YKFAISQSS
T GTVMGAVIME

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855444         401   GFYVVFDRAR KRIGFAVSAC HVHDEFRTAA VEGPFVTLD
M EDCGYNIPQT
2              401   GFYVVFDRAR KRIGFAVSAC HVHDEFRTAA VEGPFVTLD
M EDCGYNIPQT

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855444         451   DESTLMTIAY VMAAICALFM LPLCLMVCQW RCLRCLRQQ
H DDFADDISLL
2              451   DESTLMTIAY VMAAICALFM LPLCLMVCQW RCLRCLRQQ
H DDFADDISLL

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EXHIBIT 2

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855444              K
2                   K

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```

Alignment (FASTA format):
==========

>855444
MAQALPWLLLWMGAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEE
PEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFA
VGAAPHPFLHRYYQRQLSSTYRDLRKGVYEPYTQGKWEGELGTDLVSIPH
GPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS
LVKQTHVPNLFSLQLCGAGFPLNQSEVLASVGGSMIIGGIDHSLYTGSLW
YTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKK
VFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMG
EVTNQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQT
DESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRCLRQQHDDFADDISLL
K

>2
MAQALPWLLLWMGAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEE
PEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPPQTLNILVDTGSSNFA
VGAAPHPFLHRYYQRQLSSTYRDLRKGVYVPYTQGKWEGELGTDLVSIPH
GPNVTVRANIAAITESDKFFINGSNWEGILGLAYAEIARPDDSLEPFFDS
LVKQTHVPNLFSLQLCGAGFPLNQSEVLASVGGSMIIGGIDHSLYTGSLW
YTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKK
VFEAAVKSIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMG
EVTNQSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDCGYNIPQT
DESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRCLRQQHDDFADDISLL

EXHIBIT 2

K

EXHIBIT 2